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Review

The afferent signaling complex: Regulation of type I spiral ganglion neuron responses in the auditory periphery

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ABSTRACT

The spiral ganglion neurons (SGNs) are the first action potential generating neurons in the auditory pathway. The type I SGNs contact the sensory inner hair cells via their peripheral dendrites and relay auditory information to the brainstem via their central axon fibers. Individual afferent fibers show differences in response properties that are essential for normal hearing. The mechanisms that give rise to the heterogeneity of afferent responses are very poorly understood but are likely already in place at the peripheral dendrites where synapses are formed and action potentials are generated. To identify these molecular mechanisms, this review synthesizes a variety of literature and comprehensively outlines the cellular and molecular components positioned to regulate SGN afferent dendrite excitability, especially following glutamate release. These components include 1) proteins of the SGN postsynapses and neighboring supporting cells that together shape glutamatergic signaling, 2) the ion channels and transporters that determine the intrinsic excitability of the SGN afferent dendrites, and 3) the neurotransmitter receptors that extrinsically modify this excitability via synaptic input from the lateral olivocochlear efferents. This cellular and molecular machinery, together with presynaptic specializations of the inner hair cells, can be collectively referred to as the type I afferent signaling complex. As this review underscores, interactions of this signaling complex determine excitability of the SGN afferent dendrites and the afferent fiber responses. Moreover, this complex establishes the environmental milieu critical for the development and maintenance of the SGN afferent dendrites and synapses. Motivated by these important functions, this review also indicates areas of future research to elucidate the contributions of the afferent signaling complex to both normal hearing and also hearing loss.

1. Overview

The encoding of sound stimuli imposes enormous demands on the auditory system. In meeting this challenge, neurons of the auditory system show morphological, physiological, and molecular specializations that enable fast, sustained, and temporally reliable synaptic transmission over a wide dynamic range. The spiral ganglion neurons (SGNs) are the first action potential (AP) generating neurons in the auditory pathway. The central projections of these bipolar cells supply all of the auditory input from the inner hair cells (IHCs) to the central nervous system (CNS) via their axons, which are myelinated and collectively form the auditory nerve. The peripheral dendrites of the type I SGNs are unmyelinated and form synaptic contacts at the bases of these IHCs, the true sensory cells of the auditory system. Remarkably, each SGN receives input from just a single IHC via a single synapse.

While all type I SGNs exhibit extraordinary temporal precision of their sound-evoked firing, they show an enormous range in

Abbreviations: ABR, auditory brainstem response; ACh, acetylcholine; AChR, acetylcholine receptors; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AP, action potential; CAP, compound action potential; CLC, CL^- channel; CNS, central nervous system; DA, dopamine; DTX, dendrotoxin; EAAT, excitatory amino acid transporter; EPSC, excitatory postsynaptic current; EPSP, excitatory postsynaptic potential; GABA, γ-aminobutyric acid; GABAR, GABA receptor; GLAST, glutamate aspartate transporter; Glu, glutamate; GluR, glutamate receptor; GPCR, G protein-coupled receptor; GRIP, glutamate receptor interacting protein; HCN channel, hyperpolarization-activated cyclic nucleotide-gated channel; IHC, inner hair cell; ISC, inner supporting cell; KAR, kainate receptor; K_v channel, voltage gated potassium channel; LSO, lateral superior olive; LTD, long term depression; mAChR, muscarinic acetylcholine receptor; mGluR, metabotropic glutamate receptor; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; nAChR, nicotinic acetylcholine receptor; NIHL, noise-induced hearing loss; NKA, Na^+,K^+-ATPase; NMDA, N-methyl-D-aspartate; NMDAR, N-methyl-D-aspartate receptor; NSF, N-ethylmaleimide-sensitive factor; OHC, outer hair cell; PICK, protein interacting with C-kinase; PKC, protein kinase C; PSD, postsynaptic density; PSP, postsynaptic potentials; SGN, spiral ganglion neuron; TTX, tetrodotoxin; TEA, tetraethylammonium; VGCC, voltage gated Ca^{2+} channel

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threshold sensitivities and spontaneous firing rates (Liberman, 1978, 1980a). Threshold sensitivities and firing rates tend to be inversely correlated such that fibers can be generally classified as either low threshold/high spontaneous firing fibers or high threshold/low spontaneous firing fibers (Borg et al., 1988; el Barbary, 1991; Liberman, 1978; Ohlemiller and Echteler, 1990; Schmiedt, 1989; Taberner and Liberman, 2005; Tsuji and Liberman, 1997; Winter et al., 1990). Morphologically, low threshold/high spontaneous firing fibers tend to contact the pillar face of the IHCs, whereas high threshold/low spontaneous firing fibers tend to contact the modiolar faces of the IHCs as shown in cat (Liberman, 1982) and suggested by studies in guinea pig (Tsuji and Liberman, 1997) and mice (Liberman et al., 2011). Fibers on the pillar side are also generally larger in diameter and richer in mitochondria as shown in cat (Liberman, 1980b). Importantly, fiber type heterogeneity contributes to the impressive dynamic range of the auditory system.

The molecular mechanisms that endow the SGN afferent fibers with temporal fidelity and also confer heterogeneity in threshold sensitivities and spontaneous firing rates are still largely unknown. These mechanisms are undoubtedly in place at the IHC-SGN synapse and involve both pre- and postsynaptic properties. Indeed, morphological and molecular specializations at the IHC active zone have been well documented (reviewed in Glowatzki et al., 2008; Meyer and Moser, 2010; Nouvian et al., 2006; Safieddine et al., 2012). For example, differences in presynaptic ribbon size (Liberman et al., 2011; Meyer et al., 2009), presynaptic calcium channel distribution (Meyer et al., 2009), and the dynamics of vesicular release (Goutman and Glowatzki, 2007) likely regulate SGN afferent fiber responses. Underscoring their importance, the loss or dysfunction of many of the molecular components of the IHC active zone gives rise to hearing loss or deafness and has led to the identification of auditory synaptopathies (Moser et al., 2013) and hidden hearing loss (Kujawa and Liberman, 2015).

By comparison, the molecular architecture of the IHC-SGN postsynapse and SGN afferent dendrite is much less resolved. This review serves to synthesize the intrinsic and extrinsic molecular mechanisms positioned to regulate SGN afferent dendrite excitability and, thereby, shape afferent fiber firing properties. In particular, this review outlines the molecular organization and functional contributions of 1) the postsynaptic glutamate receptors and synaptic density proteins of the SGNs (Section 2), 2) the glutamate uptake machinery of the neighboring supporting cells (Section 3), 3) the voltage-gated ion channels present in the SGN afferent dendrite (Section 4), and 4) synaptic input from the lateral efferent system (Section 5). In doing so, an integrated model of the type I SGN afferent dendrite emerges in which afferent dendrite excitability and fiber firing properties are determined by the contributions from various cellular and molecular players in the auditory periphery. These players together form what can be called the type I afferent signaling complex. The functional interactions of the type I afferent signaling complex as well as areas of future research are also described (Section 6). Ultimately, examination of the larger cellular and molecular framework that establishes the type I afferent signaling complex will be required to understand the mechanisms that contribute to both normal hearing and also hearing loss.

2. Glutamate receptors and the postsynaptic density of the type i spiral ganglion neurons

Extensive evidence indicates that glutamate (Glu) mediates fast, excitatory neurotransmission between the IHCs and SGNs as part of the type I afferent signaling complex (Ottersen et al., 1998). Glutamate receptors (GluRs) are classically divided into ionotropic and metabotropic glutamate receptors. The ionotropic receptors include α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl-D-aspartate (NMDA), and kainate receptors (named after the agonists that activate them) and are all nonselective cation channels, allowing the passage of Na^+ and K^+ and, in some cases, Ca^{2+} (Traynelis et al., 2010). The metabotropic glutamate receptors (mGluRs) utilize G-protein-coupled pathways to modulate neuronal excitability and synaptic transmission, often via modulation of ion channels. Evidence (reviewed below and summarized in Table 1) suggests the presence of each of these types of GluRs in the cochlea and, in many cases, at the SGN afferent dendrite. As discussed below, differences in the distributions of these GluRs likely impart functional differences in afferent dendrite excitability and contribute to auditory synaptopathies and hidden hearing loss.

2.1. AMPA receptors

AMPA receptors are tetramers made up of homomeric or heteromeric combinations of four subunits: GluA1-4 (Traynelis et al., 2010). Patch clamp recordings of the type I SGN afferent dendrite convincingly show that excitatory postsynaptic currents (EPSCs) are AMPA-mediated (Glowatzki and Fuchs, 2002; Grant et al., 2010). GluA2 and 3 (Hakuba et al., 2003; Huang et al., 2012; Knipper et al., 1997; Luo et al., 1995; Matsubara et al., 1996; Ryan et al., 1991; Safieddine and Eybalin, 1992) and possibly GluA4 (Eybalin et al., 2004; Furness and Lawton, 2003; Hakuba et al., 2003; Huang et al., 2012; Knipper et al., 1997; Kuriyama et al., 1994; Matsubara et al., 1996) are present in SGN afferent dendrites in the adult cochlea. GluA1 is believed to be lost during development (Eybalin et al., 2004). The kinetics and amplitudes of the excitatory synaptic responses are determined by the density of receptor expression and the receptor subunit composition (Traynelis et al., 2010). Perhaps not surprisingly then, SGN afferent dendrites in the mature mouse cochlea show pillar-modiolar gradients in the size of GluA patches that correlate with differences in fiber thresholds and firing rates (Liberman and Liberman, 2015; Liberman et al., 2011; Yin et al., 2014).

In the CNS, additional variation in GluA-mediated synaptic responses is caused by pre- and post-translational regulation. First, RNA editing of the GluA2 transcript (prior to RNA splicing) at position 607 (the QRN site) results in replacement of glutamine (Q) with arginine (R) and likely changes the electrostatics in the receptor pore by introducing an additional positive charge. This amino acid change prevents Ca^{2+} permeability, removes block by endogenous intracellular polyamines, and reduces the single-channel conductance. Thus, the GluA2 subunit determines critical biophysical properties of GluAs *in vivo* (Isaac et al., 2007). Q to R editing of GluA2 in the SGNs has not been investigated directly. However, there is some evidence to suggest that AMPA receptors in SGNs may be Ca^{2+} permeable (Eybalin et al., 2004; Morton-Jones et al., 2008). Second, for all GluA subunits, alternative splicing results in either flip or flop versions that affect receptor kinetics. Both flip and flop mRNA for GluA2, A3, and A4 have been identified in adult rat SGNs (Niedzielski and Wenthold, 1995). Finally, phosphorylation of GluAs regulates their trafficking and membrane expression (Malinow and Malenka, 2002) and may be one mechanism by which pillar-modiolar gradients in GluA expression are maintained in the SGNs.

2.2. Kainate receptors

Kainate receptors (KARs) are another class of ionotropic glutamate receptors and are divided into five classes: GluK1-5 (Collingridge et al., 2009). Although experiments suggest that

Table 1
Glutamate receptors regulating excitability of the type I spiral ganglion neurons.

Identity	Species	Location	Detection method[a]	Reference
GluA1	Rat	Cochlea (≤P10)	WB	Eybalin et al., 2004
	Rat	Soma (≤P10)	IHC	Knipper et al., 1997
No GluA1	Rat	Soma (˃P10)	WB, IHC	Knipper et al., 1997
	Rat	Soma	ISH	Luo et al., 1995
	Rat	Postsynaptic density	Immuno-EM	Matsubara et al., 1996
	Rat	Sprial ganglion, soma	rtPCR, ISH, IHC	Niedzielski and Wenthold, 1995
	Rat	Soma	ISH	Ryan et al., 1991
	Rat, guinea pig	Soma	ISH	Safieddine and Eybalin, 1992
GluA2	Rat	Likely afferent dendrites	IHC	Eybalin et al., 2004
	Rat	Cochlea (≥P10)	WB	Eybalin et al., 2004
	Rat	Postsynaptic density	IHC	Fujikawa et al., 2014
	Guinea pig	Postsynaptic density	IHC	Furman et al., 2013
	Rat	Soma	ISH	Luo et al., 1995
	Rat	Spiral ganglion, soma	rtPCR, ISH	Niedzielski and Wenthold, 1995
	Rat	Soma	ISH	Ryan et al., 1991
	Rat, guinea pig	Soma	ISH	Safieddine and Eybalin, 1992
GluA3	Rat	Cochlea	WB	Eybalin et al., 2004
	Rat	Soma	ISH	Luo et al., 1995
	Rat	Spiral ganglion, soma	rtPCR, ISH	Niedzielski and Wenthold, 1995
	Rat	Soma	ISH	Ryan et al., 1991
	Rat, guinea pig	Soma	ISH	Safieddine and Eybalin, 1992
GluA2/3	Gerbil	Postsynaptic density	Immuno-EM	Hakuba et al., 2003
	Mouse	Postsynaptic density	IHC	Huang et al., 2012
	Rat	Soma	WB, IHC	Knipper et al., 1997
	Rat	Soma	IHC	Kuriyama et al., 1994
	Mouse	Postsynaptic density	IHC	Liberman et al., 2011
	Rat	Postsynaptic density	Immuno-EM	Matsubara et al., 1996
	Rat	Soma	IHC	Niedzielski and Wenthold, 1995
	Rat, guinea pig, monkey	Soma	IHC	Usami et al., 1995
GluA4	Rat	Cochlea	WB	Eybalin et al., 2004
	Guinea pig	Likely Postsynaptic density	IHC	Furness and Lawton, 2003
	Gerbil	Postsynaptic density	Immuno-EM	Hakuba et al., 2003
	Mouse	Postsynaptic density	IHC	Huang et al., 2012
	Rat	Soma	WB, IHC	Knipper et al., 1997
	Rat	Soma, likely Postsynaptic density	IHC	Kuriyama et al., 1994
	Rat	Soma (≤P21)	ISH	Luo et al., 1995
	Rat	Postsynaptic density	Immuno-EM	Matsubara et al., 1996
	Rat	Spiral ganglion, soma	rtPCR, ISH	Niedzielski and Wenthold, 1995
No GluA4	Rat	Soma	ISH	Ryan et al., 1991
	Rat, guinea pig	Soma	ISH	Safieddine and Eybalin, 1992
GluK1	Rat	Spiral ganglion, soma	rtPCR, ISH	Niedzielski and Wenthold, 1995
	Mouse	Cochlea, Postsynaptic density	qPCR, IHC	Peppi et al., 2012
No GluK1	Rat	Soma	ISH	Luo et al., 1995
	Rat	Soma	ISH	Ryan et al., 1991
GluK2	Rat	Postsynaptic density	IHC	Fujikawa et al., 2014
	Rat	Soma (≤P21)	ISH	Luo et al., 1995
	Rat	Spiral ganglion, soma	rtPCR, ISH	Niedzielski and Wenthold, 1995
	Mouse	Cochlea, Postsynaptic density	qPCR, IHC	Peppi et al., 2012
GluK3	Mouse	Cochlea, Postsynaptic density	qPCR, IHC	Peppi et al., 2012
No GluK3	Rat	Spiral ganglion	rtPCR	Niedzielski and Wenthold, 1995
GluK4	Rat	Spiral ganglion, soma	rtPCR, ISH	Niedzielski and Wenthold, 1995
	Mouse	Cochlea, Postsynaptic density	qPCR, IHC	Peppi et al., 2012
GluK5	Mouse, rat	Soma, Postsynaptic density	*lacZ* expression (mouse), IHC (rat)	Fujikawa et al., 2014
	Rat	Spiral ganglion, soma	rtPCR, ISH	Niedzielski and Wenthold, 1995
	Mouse	Cochlea, Postsynaptic density	qPCR, IHC	Peppi et al., 2012
GluN1	Rat	Soma	WB, IHC	Knipper et al., 1997
	Rat	Spiral ganglion, soma	rtPCR, ISH, IHC	Niedzielski and Wenthold, 1995
	Rat	Cochlea, Postsynaptic density	WB, IHC, Immuno-EM	Ruel et al., 2008
	Rat, guinea pig, monkey	Soma	IHC	Usami et al., 1995
GluN2A	Rat	Soma (≤P10)	WB, IHC	Knipper et al., 1997
No GluN2A	Rat	Soma (˃P10)	WB, IHC	Knipper et al., 1997
GluN2B	Rat	Cochlea	WB	Ruel et al., 2008
GluN2A/B	Rat	Spiral ganglion, soma	IHC	Niedzielski and Wenthold, 1995
	Rat	Postsynaptic density	Immuno-EM	Ruel et al., 2008
GluN2C	Rat	Cochlea	WB	Ruel et al., 2008
No GluN2C	Rat	Soma	IHC	Knipper et al., 1997
GluN2D	Rat	Cochlea	WB	Ruel et al., 2008
GluN2A-D	Rat	Spiral ganglion, soma	rtPCR, ISH	Niedzielski and Wenthold, 1995
mGluR1	Rat	Soma	ISH	Safieddine and Eybalin, 1995
mGluR7	Human, mouse	Soma, IHC region	IHC (human and mouse), ISH (mouse only)	Friedman et al., 2009

[a] IHC = immunohistochemistry, ISH = in situ hybridization, rtPCR = reverse transcriptase PCR, WB = western blot, EM = electron microscopy.

GluKs do not contribute to afferent activity *in vivo* (Ruel et al., 2000) or shape the spontaneous EPSC *in vitro* (Glowatzki and Fuchs,

2002), a recent study found that cochlear perfusion of a GluK1 antagonist reduced the compound action potential (CAP) in a concentration-dependent manner (Peppi et al., 2012) All five KARs have been detected in the afferent dendrites and colocalized with GluA2 (Peppi et al., 2012), although other evidence suggests the absence of GluK3 (Fujikawa et al., 2014; Niedzielski and Wenthold, 1995). In addition to postsynaptic expression, Fujikawa and colleagues reported the additional presynaptic (IHC active zone) expression of GluK2 (Fujikawa et al., 2014). The relative abundances of GluKs and GluA2 appear to differ, with some dendrites expressing more of one receptor type and less of another (Peppi et al., 2012).

A number of features distinguish GluKs from GluAs (Lerma and Marques, 2013) and may have important consequences for their functional expression in the SGN afferent dendrites. First, GluK-mediated EPSCs are characteristically slower and smaller than GluA-mediated EPSCs. Second, GluK opening requires external ion binding. Third, GluKs, which are canonically considered ionotropic receptors, can also act as unconventional metabotropic receptors involving G proteins through as yet unclear mechanisms (Lerma and Marques, 2013). Thus, GluKs may contribute postsynaptically to the heterogeneity of excitatory postsynaptic potentials (EPSPs) recorded from the SGN afferent dendrites (Glowatzki and Fuchs, 2002; Grant et al., 2010) as proposed by Peppi et al. (2012). In the CNS, postsynaptic KARs have been shown to regulate neuronal excitability by modulating the afterhyperpolarization current (Melyan et al., 2002, 2004). Such a mechanism might regulate firing rate of the SGNs. Finally, KARs have been shown to presynaptically modulate glutamate and γ-aminobutyric acid (GABA) release (Lerma, 2003). Thus, KARs may shape release from the IHCs or lateral efferent terminals and, thereby, metabotropically modulate afferent dendrite excitability.

2.3. NMDA receptors

NMDA receptors (NMDARs: GluN1, GluN2A-D, and GluN3A-B) are ligand-gated cation channels permeable to K^+, Na^+, and Ca^{2+} and activated by extracellular glutamate and the co-agonist glycine (Traynelis et al., 2010). They are also voltage-gated in that extracellular Mg^{2+} blocks the channel at negative membrane potentials. In the CNS, NMDARs do not contribute to fast synaptic transmission despite their colocalization with AMPARs and KARs and their high affinity for glutamate. First, at resting membrane potentials they are blocked by extracellular Mg^{2+} (which is only dislodged by significant depolarization). Second, they activate much more slowly than either AMPARs or KARs. In the cochlea, studies suggest that NMDARs do not contribute to synaptic transmission at the type I SGN synapse (Glowatzki and Fuchs, 2002; Ruel et al., 1999). Even so, a variety of NMDAR subunits have been identified specifically in SGNs (Knipper et al., 1997; Ruel et al., 2008; Usami et al., 1995), and they may be involved in development and regrowth of SGN afferent dendrites (Bartlett and Wang, 2013; Ruel et al., 2007). An excellent recent review of NMDARs in the auditory pathway (Sanchez et al., 2015) highlights the need for more research.

2.4. Metabotropic glutamate receptors

Metabotropic glutamate receptors (mGluRs) modulate neuronal excitability and synaptic transmission via G protein-coupled pathways and are divided into 3 groups (group I: mGluR1 and 5, group II: mGluR2 and 3, and group III: mGluR 4,6,7, and 8) (Niswender and Conn, 2010). Although mGluRs do not mediate fast synaptic transmission, they can mediate changes in excitability through the modification of other proteins, including ion channels, and thereby modulate synaptic transmission over longer timescales (Durand et al., 2008; Nicoletti et al., 2011). Given their diverse subcellular localizations (both pre- and postsynaptic) and signaling pathways, predicting the contribution of mGluRs to afferent dendrite excitability is difficult. Evidence suggests the presence of both group I and group III mGluRs in the SGNs but functional analysis of their excitatory or inhibitory role is contradictory (reviewed in Lu, 2014). Recent identification of the involvement of mGluR7 in age-related hearing loss is further motivation for better understanding of mGluR signaling in the auditory periphery (Friedman et al., 2009).

2.5. The postsynaptic density

The postsynaptic density (PSD) is a highly specialized, macromolecular structure that has been extensively studied in glutamatergic synapses in the CNS (reviewed in Okabe, 2007; Sheng and Hoogenraad, 2007) but much less so in the cochlea. The PSD is essential for synaptic transmission and serves to juxtapose glutamate receptors to presynaptic sites of neurotransmitter release and also cluster a variety of intracellular signaling proteins, including phosphatases, kinases, scaffolding proteins, and cytoskeleton proteins (Sheng and Hoogenraad, 2007). In many ways, PSDs of the SGNs appear morphologically (Nouvian et al., 2006; Sobkowicz et al., 1982) and molecularly (Braude et al., 2015; Davies et al., 2001; Huang et al., 2012) similar to those of the CNS. Several conserved PSD proteins are present in the postsynaptic terminal underneath the IHC (see also Table 6), namely PSD-93 (Davies et al., 2001), PSD-95 (Braude et al., 2015; Davies et al., 2001), and Shank1 (Braude et al., 2015; Huang et al., 2012). Although not extensively investigated, these proteins may be organized differently within the SGN PSDs compared to their CNS counterparts: ultrastructural examination of GluA (2–4) distribution revealed greater concentrations of receptors peripherally rather than centrally along the length of the PSD (Matsubara et al., 1996). Ring-like distribution of AMPARs in the PSD was also identified using STED microscopy (Chapochnikov et al., 2014; Meyer et al., 2009). In the CNS, the PSD also tethers NMDARs and mGluRs in specific locations relative to AMPARs (reviewed in Sheng and Hoogenraad, 2007).

The functional contributions of PSD proteins in the SGN afferent dendrites have only been examined in Shank1 knockout mice (Braude et al., 2015). Shank proteins (1–3) serve as the central PSD scaffold in the CNS (Sheng and Kim, 2000), and Shank1 (and likely not 2 and 3) is present in the SGN PSDs in the mature cochlea (Braude et al., 2015; Huang et al., 2012). Despite changes in PSD structure and glutamatergic signaling seen in the CNS upon loss of Shank1, SGN afferent synapse structure and function seem relatively intact (Braude et al., 2015). This surprising result suggests that the SGN PSDs (like their presynaptic ribbon active zones) simply may not require the same repertoire of synaptic proteins that are indispensable in the CNS and/or they may use unconventional proteins not found in the CNS.

Nonetheless, the SGN postsynapses in the cochlea undergo compositional changes in GluA during development and may retain elements of plasticity after maturation that are both reminiscent of processes orchestrated by PSDs in the CNS (Chater and Goda, 2014). For example, GluA subunit expression in the cochlea appears to be developmentally regulated (Eybalin et al., 2004; Knipper et al., 1997) and may shape firing properties (as suggested by Grant et al., 2010). Furthermore, even after development, evidence suggests that GluA trafficking is still plastic: application of glutamate receptor agonists in cultured SGNs or acoustic stimulation *in vivo* causes a reversible reduction of surface GluA2 receptors in the SGNs or cochlea (Chen et al., 2007). Such dynamic regulation of GluAs is similar to long term depression (LTD) in the CNS, and also seems to involve clathrin-mediated endocytosis of GluAs (Chen et al., 2009). Finally, gradients in GluA distribution in the

Table 2
Voltage-gated sodium channels regulating intrinsic excitability of the spiral ganglion neurons.

Identity	Species	Location	Detection method[a]	Reference
$Na_V1.1$	Rat	Soma, afferent dendrites	rtPCR, IHC	Fryatt et al., 2009; Kim and Rutherford, 2016
No $Na_V1.2$	Rat	Spiral ganglion	rtPCR	Fryatt et al., 2009
	Mouse	Afferent dendrites	IHC	Hossain et al., 2005
No $Na_V1.3$	Rat	Spiral ganglion	rtPCR	Fryatt et al., 2009
$Na_V1.6$	Rat	Soma	rtPCR, IHC	Fryatt et al., 2009; Kim and Rutherford, 2016
	Mouse	Afferent dendrite heminode	IHC	Hossain et al., 2005
$Na_V1.7$	Rat	Soma	rtPCR, IHC	Fryatt et al., 2009
No $Na_V1.8$	Rat	Soma	rtPCR	Fryatt et al., 2009
No $Na_V1.9$	Rat	Spiral ganglion	rtPCR	Fryatt et al., 2009

[a] rtPCR = reverse transcriptase PCR, IHC = immunohistochemistry.

Table 3
Voltage-gated potassium channels regulating intrinsic excitability of the spiral ganglion neurons.

Identity	Species	Location	Detection method[a]	Reference
$K_V1.1$	Mouse	Soma, afferent dendrites	IHC, qPCR, pharmacology	Crozier and Davis, 2014 Oak and Yi, 2014 [b] Rusznak and Szucs, 2009 [b]; Kim and Rutherford, 2016
$K_V1.2$	Mouse	Soma, afferent dendrite	IHC	Oak and Yi, 2014 [b] Rusznak and Szucs, 2009 [b]
$K_V1.4$	Mouse	Soma	IHC	Oak and Yi, 2014 [b] Rusznak and Szucs, 2009 [b]
$K_V1.2$/1.4 heteromultimers	Mouse	Soma	Pharmacology	Wang et al., 2013
$K_V1.6$	Guinea pig	Soma	IHC	Rusznak and Szucs, 2009 [b]
KV2.2	Rat	Afferent dendrite	IHC	Kim and Rutherford, 2016
$K_V3.1$	Mouse, rat	Soma, afferent dendrite	IHC, qPCR	Oak and Yi, 2014 [b] Rusznak and Szucs, 2009 [b]; Kim and Rutherford, 2016
No $K_V3.2$	Guinea pig	Soma	IHC	Rusznak and Szucs, 2009 [b]
$K_V3.4$	Guinea pig	Soma	IHC	Rusznak and Szucs, 2009 [b]
$K_V4.2$	Guinea pig	Soma	IHC	Oak and Yi, 2014 [b] Rusznak and Szucs, 2009 [b]
$K_V4.3$	Guinea pig	Soma	IHC	Rusznak and Szucs, 2009 [b]
$K_V7.2$	Guinea pig, mouse, rat	Soma, afferent dendrites	IHC, rtPCR	Jin et al., 2009; Kim and Rutherford, 2016
$K_V7.3$	Guinea pig, mouse, rat	Soma, afferent dendrites	IHC, rtPCR	Jin et al., 2009; Kim and Rutherford, 2016
$K_V7.4$	Mouse	Soma	IHC	Beisel et al., 2005
$K_V11.1$	Mouse	Soma	IHC	Oak and Yi, 2014 [b]

[a] IHC = immunohistochemistry, qPCR = quantitative reverse transcriptase PCR, rtPCR = reverse transcriptase PCR.
[b] Review articles.

Table 4
Voltage-gated calcium channels regulating intrinsic excitability of the spiral ganglion neurons.

Identity	Species	Location	Detection method[a]	Reference
No $Ca_V1.1$	Mouse	Spiral ganglion	qPCR	Chen et al., 2011
$Ca_V1.2$	Mouse	Soma	qPCR, IHC	Chen et al., 2011
	Chinchilla	Soma, afferent dendrites	IHC	Lopez et al., 2003
	Mouse	Soma	IHC	Lv et al., 2014
	Rat	Soma	IHC	Roehm et al., 2008
$Ca_V1.3$	Mouse	Soma	qPCR, IHC	Chen et al., 2011
	Chinchilla	Soma	IHC	Lopez et al., 2003
	Mouse	Soma	IHC	Lv et al., 2014, 2012
No $Ca_V1.4$	Mouse	Spiral ganglion	qPCR	Chen et al., 2011
No $Ca_V2.1$	Chinchilla	Soma	IHC	Lopez et al., 2003
CaV2.1	Mouse	Soma	qPCR, IHC	Chen et al., 2011
	Mouse	Soma	IHC	Lv et al., 2012
	Rat	Soma	IHC	Roehm et al., 2008
$Ca_V2.2$	Mouse	Soma	qPCR, IHC	Chen et al., 2011
	Chinchilla	Soma	IHC	Lopez et al., 2003
	Mouse	Soma	IHC	Lv et al., 2012
	Rat	Soma	IHC	Roehm et al., 2008
$Ca_V2.3$	Mouse	Soma	qPCR, IHC	Chen et al., 2011
	Chinchilla	Soma	IHC	Lopez et al., 2003
	Mouse	Soma	IHC	Lv et al., 2012
$Ca_V3.1$	Mouse	Soma	qPCR, IHC	Chen et al., 2011
	Mouse	Soma	IHC	Lv et al., 2012
$Ca_V3.2$	Mouse	Spiral ganglion	qPCR	Chen et al., 2011
	Mouse	Soma	IHC	Lv et al., 2012
$Ca_V3.3$	Mouse	Soma	qPCR, IHC	Chen et al., 2011
	Mouse	Soma	IHC	Lv et al., 2012

[a] qPCR = quantitative reverse transcriptase PCR, IHC = immunohistochemistry.

Table 5
Lateral efferent neurotransmitter receptors regulating excitability of the spiral ganglion neurons.

Identity	Species	Location	Detection method[a]	Reference
D1	Rat	Soma	rtPCR (cochlea), IHC	Inoue et al., 2006
	Mouse	Soma, afferent dendrites	rtPCR, qPCR, IHC	Maison et al., 2012
	Guinea pig	Soma, likely afferent dendrites	IHC	Niu and Canlon, 2006
D1-like (D1 and D5)	Rat	Soma, likely afferent dendrites	IHC	Inoue et al., 2006
	Mouse	Soma	Pharmacology	Sun and Salvi, 2001
	Rat	Soma	Pharmacology	Valdes-Baizabal et al., 2015
D2	Rat	Soma	rtPCR (cochlea), IHC	Inoue et al., 2006
	Mouse	Soma, afferent dendrites	rtPCR, qPCR, IHC	Maison et al., 2012
D2-like (D2,3,4)	Rat	Soma, likely afferent dendrites	IHC	Inoue et al., 2006
	Mouse	Soma	Pharmacology	Sun and Salvi, 2001
	Rat	Soma	Pharmacology	Valdes-Baizabal et al., 2015
D3	Rat	Soma	rtPCR (cochlea), IHC	Inoue et al., 2006
No D3	Mouse	Soma	rtPCR, qPCR	Maison et al., 2012
D4	Rat	Soma	rtPCR (cochlea), IHC	Inoue et al., 2006
	Mouse	Soma	rtPCR, qPCR	Maison et al., 2012
D5	Rat	Soma	rtPCR (cochlea), IHC	Inoue et al., 2006
	Mouse	Soma	rtPCR, qPCR	Maison et al., 2012
nAChR (α5-7, β2-3)	Rat	Spiral ganglion	rtPCR	Morley et al., 1998
nAChR (α6-7, β2)	Rat	Soma	ISH	Morley et al., 1998
nAChR (β2)	Mouse	Soma	rtPCR, IHC	Tang et al., 2014
M1	Rat	Soma (also inner hair cells)	IHC	Khan et al., 2002
No M1	Mouse	Soma	rtPCR, qPCR	Maison et al., 2010
M2	Mouse	Soma, likely LOC efferent terminals	rtPCR, qPCR, IHC	Maison et al., 2010
No M2	Rat	Soma	IHC	Khan et al., 2002
M3	Rat	Soma (also inner hair cells)	IHC	Khan et al., 2002
	Rat, guinea pig	Soma	rtPCR, ISH	Safieddine et al., 1996
No M3	Mouse	Soma	rtPCR, qPCR	Maison et al., 2010
M4	Mouse	Soma	rtPCR, qPCR	Maison et al., 2010
No M4	Rat	Soma	IHC	Khan et al., 2002
M5	Rat	Soma (also inner hair cells)	IHC	Khan et al., 2002
	Mouse	Soma	rtPCR, qPCR	Maison et al., 2010
$GABA_A$	Mouse	Soma	Pharmacology	Lin et al., 2000
	Rat	Soma	Pharmacology	Malgrange et al., 1997
	Guinea pig	Soma	Pharmacology	Nakagawa et al., 2005
$GABA_A$ α1-6, β1-3, and γ subunits	Rat	Soma, likely afferent dendrites	IHC	Yamamoto et al., 2002
$GABA_A$ α1 subunit	Mouse	Soma	rtPCR, IHC	Tang et al., 2014
$GABA_A$ β3 subunit	Mouse	Soma	IHC	Maison et al., 2006
$GABA_B$	Mouse	Soma	Pharmacology, qPCR	Lin et al., 2000
$GABA_{B1}$	Mouse	Soma, likely afferent dendrites	GFP-tagged $GABA_{B1}$	Maison et al., 2009

[a] IHC = immunohistochemistry, ISH = in situ hybridization, rtPCR = reverse transcriptase PCR, qPCR = quantitative reverse transcriptase PCR.

Table 6
Summary of the postsynaptic elements of the type I afferent signaling complex (Elements of ribbon synapses are reviewed elsewhere as referenced in the Overview.).

Identity	Species	Location	Detection method[a]	Reference
HCN (1, 2, and 4)	Rat	SGN afferent dendrites	Pharmacology, IHC	Yi et al., 2010
Na^+,K^+-ATPase α3	Rat	SGN afferent dendrites	IHC	McLean et al., 2009
Na^+,K^+-ATPase α1	Rat	Inner supporting cells	IHC	McLean et al., 2009
Postsynaptic density-93	Rat	Postsynaptic density	rtPCR (organ of Corti), IHC, Immuno-EM	Davies et al., 2001
Postsynaptic density-95	Rat	Postsynaptic density	rtPCR (organ of Corti), IHC, Immuno-EM	Davies et al., 2001
	Mouse	Postsynaptic density	IHC	Braude et al., 2015
Shank1	Mouse	Postsynaptic density	IHC	Huang et al., 2012
	Mouse	Postsynaptic density	qPCR (cochlea), IHC	Braude et al., 2015
EAAT1	Rat, guinea pig	Inner supporting cells	IHC, Immuno-EM, Pharmacology	Furness and Lehre, 1997, 2003; Glowatzki et al., 2006

[a] IHC = immunohistochemistry, rtPCR = reverse transcriptase PCR, qPCR = quantitative reverse transcriptase PCR, EM = electron microscopy.

postsynapse that may underlie differences in the firing properties of fibers (Liberman et al., 2011) likely depend on the PSD and, interestingly, disappear following de-efferentation (Yin et al., 2014). Thus, PSDs in the cochlea may serve as important regulators of synaptic transmission in response to both intracellular and extracellular signals. These findings collectively motivate further characterization of the molecular composition of the cochlear afferent PSD.

3. Glutamate uptake by neighboring supporting cells

Intense glutamate release or insufficient removal of glutamate causes glutamate accumulation within the synaptic space enclosed by the afferent signaling complex. This accumulation can lead to desensitization of the AMPA receptors and activation of extrasynaptic AMPA (and other glutamate) receptors. Thus, glutamate accumulation can degrade the fidelity of glutamatergic signaling (see Barbour and Hausser, 1997) and potentially lead to excitotoxic cell death (Kostandy, 2012). Therefore, extracellular levels of glutamate are strictly regulated, and glutamate is removed from the synaptic space by both passive diffusion as well as active transport by neighboring cells. These glutamate transporters include the excitatory amino acid transporters or EAATs 1-5. In rodents, EAAT1-3 also go by the names glutamate aspartate transporter (GLAST),

GLT1, and EAAC1, respectively (Jensen et al., 2015).

In the cochlea, supporting cells surrounding the inner hair cell and afferent synapses express GLAST/EAAT1 (Furness and Lehre, 1997; Furness and Lawton, 2003; Li et al., 1994; Rebillard et al., 2003) that mediates glutamate transporter currents from the inner phalangeal cells of the rodent cochlea (Glowatzki et al., 2006). EAAT1 knockout mice show slightly but significantly elevated auditory brainstem response (ABR) thresholds compared to wild-type mice and, importantly, increased sensitivity to noise-induced hearing loss (NIHL; Hakuba et al., 2000). These findings are consistent with reports of glutamate excitotoxicity in the cochlea (reviewed in Pujol and Puel, 1999). Recent work examining the effects of cochlear perfusion of various glutamate transporter blockers on CAP thresholds showed changes in thresholds and recoveries only when transporter blockers were applied with additional glutamate or noise challenges (Chen et al., 2010). All together these findings indicate that glutamate transporters may not play a critical role in auditory function under quiet or moderate noise levels but may ameliorate NIHL following acoustic overexposure.

4. Voltage-gated ion channels and ion transporters of the type i spiral ganglion neurons

Voltage-gated ion channels are transmembrane proteins that open in response to changes in the membrane potential and allow the passive flow of ions across the cell membrane. The complement of postsynaptic voltage-gated ion channels will shape the postsynaptic potentials (PSPs), and determine action potential (AP) output (Magee and Johnston, 2005). Patch clamp electrophysiology has been essential to investigating the voltage-gated ion channels present in excitable cells. Although extremely difficult to perform, patch clamp recordings of SGN afferent boutons from P7-14 rats (Yi et al., 2010) revealed various conductances in response to membrane depolarization, including a tetrodotoxin (TTX)-sensitive Na^+ conductance, a cadmium-sensitive Ca^{2+} conductance, and 4-AP and tetraethylammonium (TEA)-sensitive K^+ conductances (Yi et al., 2010). Exciting recent work by Kim and Rutherford, examined maturation of voltage-gated sodium and potassium channels in the SGN afferent dendrites using immunofluorescence (2016). Their work is significant progress in determining the molecular identities and subcellular locations of ion channels that shape spike generation in SGNs. Much more work investigating the voltage-gated ion channels present in SGNs has come from isolated or cultured SGNs. These experiments do not *per se* examine the repertoire of ion channels specifically in the peripheral processes and cannot rule out changes in ion channel expression or distribution as a result of isolation or culturing. Nevertheless, evidence gathered from SGN afferent dendrites (although still under-investigated), isolated SGNs, and synapses of the auditory brainstem suggest that a similar repertoire of voltage-gated ion channels is positioned along the length of the auditory pathway and serves to maintain fast, sustained, and temporally reliable synaptic transmission (see Tables 2–4). In the SGN afferent dendrites, a core set of voltage-gated ion channels likely enable fast, repetitive spiking with subtle changes in subtypes and distribution tailoring the individual differences in thresholds and firing rates. In this context, this section reviews what is known about the major classes of voltage-gated ion channels that are important for maintenance of the resting potential, shaping the excitatory PSP (EPSP), and initiating APs. This information updates other comprehensive reviews (Davis and Liu, 2011; Oak and Yi, 2014; Rusznak and Szucs, 2009).

4.1. Voltage-gated sodium channels

Voltage-gated sodium channels (VGSCs) are traditionally classified into nine families ($Na_V1.1$-1.9) (Catterall et al., 2005). While VGSCs share a similar structure and generally serve to initiate APs in excitable cells, their localization, associated regulatory subunits, and pharmacology can vary considerably (Catterall et al., 2005). TTX sensitive Na^+ currents have been identified using patch clamp recordings from acutely dissociated SGNs in guinea pig (Santos-Sacchi, 1993) and rats (Moore et al., 1996) as well as cultured SGNs from newborn gerbils (Lin, 1997).

More recent work has identified the particular subunits that might be involved in normal and pathological function of the SGN afferent dendrites. Early immunofluorescence in cochlear sections from adult mice (3–4 month old) showed robust Pan Na_V and specifically $Na_V1.6$ (but not $Na_V1.2$) immunoreactivity in both the peripheral axonal initial segments and subsequent nodes in the SGN processes (Hossain et al., 2005). This work also showed disrupted $Na_V1.6$ localization in the deaf mutant quivering mouse, suggesting that $Na_V1.6$ is, in particular, necessary for normal hearing. Its presence at sites of AP generation in the SGNs is not surprising given that $Na_V1.6$ is known to be important for AP generation and localized to the axon initial segment and nodes of Ranvier in various neurons (O'Brien and Meisler, 2013).

Subsequent work has used immunocytochemistry to localize $Na_V1.6$ and $Na_V1.7$ to SGN somas and $Na_V1.1$ particularly to the SGN axonal processes (Fryatt et al., 2009). Later work from this group used qPCR and immunohistochemistry to document changes in VGSC expression and distribution following noise trauma in rats. In particular, they report increased immunoreactivity for $Na_V1.1$ along the SGN peripheral dendrites and $Na_V1.7$ in the SGN somas following noise exposure (Fryatt et al., 2011). These results suggest that changes in VGSC subunits in the SGNs may also contribute to the auditory pathologies following noise exposure, such as tinnitus and hyperacusis. Finally, very recent work by Kim and Rutherford used immunfluorescence to examine the maturation of NaV1.1 and NaV1.6 expression in the spike-initiating heminode of rat SGN afferent dendrites. These authors suggest that consolidation of NaV1 expression in the heminode may underlie the decreased latency and increased synchrony of afferent fiber firing observed in the weeks after hearing onset.

A summary of the Na_V channels identified in the SGNs is provided in Table 2.

4.2. Voltage-gated potassium channels

Voltage-gated potassium channels (K_V1-12) are structurally and functionally diverse and collectively represent the largest family of all potassium channels (Gutman et al., 2003). As in other excitable cells, voltage-gated potassium channels are poised to set and restore the resting membrane potential of the SGN. Molecular identification of K_V channels is difficult considering their genetic diversity. Nevertheless, a number of K_V channels (including Kv1.1, 1.2, 1.4, 1.6, 3.1, 3.3, 3.4, 4.2, 4.3, 7.2, 7.3, 7.4, and 11.1) have been detected in SGNs as reviewed previously (Oak and Yi, 2014; Rusznak and Szucs, 2009). The role of potassium channels in regulating temporal precision along the auditory pathway is particularly well reviewed by Oak and Yi (Oak and Yi, 2014). More recent work has added to our understanding of the biophysical roles of K_V1 and $K_V4.2$ and characterized K_V7 in SGNs. Particularly notable work by Kim and Rutherford used immunofluorescence to examine the distribution of KV1.1, 3.1b, 7.2, and 7.3 in the rat SGN afferent dendrites (2016). A summary of the K_V channels identified in the SGNs is provided in Table 3.

$K_V1.1$ (Crozier and Davis, 2014; Liu et al., 2014b) and $K_V1.2$ (Liu et al., 2014b) appear to be developmentally and tonotopically regulated in SGNs cultured from mice. KV1.1 has been localized by immunofluorescence to juxtanodes in the rat SGN afferent

dendrites (Kim and Rutherford, 2016). Application of dendrotoxin (DTX,a blocker of K_V1.1, 1.2, and 1.6) depolarizes the resting membrane potential and reduces AP threshold of cultured SGNs (Liu et al., 2014b). The developmental acquisition of K_V1 may be important in fine tuning SGN excitability and firing rate. Paradoxically, SGNs cultured from K_V1.2 knockout mice were found to be more hyperpolarized and less excitable than SGNs from wildtype mice (Wang et al., 2013). These authors provide evidence that K_V1.2 is normally found as a heteromultimer with K_V1.4. K_V1.2/1.4 heteromultimers require greater membrane depolarization for activation and are also remarkably insensitive to DTX (Wang et al., 2013), which suggests careful re-interpretation of previous work examining DTX-sensitive currents in SGNs.

Recent work using immunofluorescence in the mature rat organ of Corti has also shown that KV channels have very specific subcellular distributions in the SGN afferent dendrite (Kim and Rutherford, 2016). In particular, KV3.1b is localized to nodes and heminodes whereas KV2.2 is present in juxtanodes. KV7.2 and KV7.3 appear to be present in the entire unmyelinated SGN afferent dendrite just below the base of the IHCs. K_V4.2 has been identified in cultured SGNs (Adamson et al., 2002a, 2002b) and may interact with the β subunit KCNE3 to regulate the SGN resting membrane potential, AP threshold, and AP duration (Wang et al., 2014b). In sections of the adult guinea pig cochlea K_V7.2 (KCNQ2) immunoreactivity was specifically observed in the unmyelinated portion of the SGN afferent dendrite (Jin et al., 2009), consistent with observations of Kim and Rutherford (2016). K_V7.4 (KCNQ4), which is associated with progressive high frequency hearing loss (DFNA2), shows expression in the outer hair cells but also SGN somas (Beisel et al., 2005). Recent work shows that blockade of K_V7s (and likely K_V7.4) in SGNs cultured from mice reduces the resting membrane potential and may, thereby, initiate Ca^{2+}-mediated apoptotic SGN death that underlies or contributes to the degeneration of the SGNs seen as part of the DFNA2 auditory phenotype (Lv et al., 2010).

4.3. HCN channels

As their name indicates, the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are activated by membrane hyperpolarization, with activation often facilitated by their intracellular interaction with cyclic nucleotides (especially cAMP). They are non-selective cation channels permeable to Na^+ and K^+ and, therefore, serve to depolarize the cell membrane in response to hyperpolarization (Benarroch, 2013). The four members (HCN1–4) can form homotetramers or heterotetramers, with individual HCN subunits determining the biophysical properties, including voltage activation, kinetics, and gating by cyclic nucleotides. Extensive evidence suggests that HCN channels are present in the SGNs (Bakondi et al., 2009; Chen, 1997; Kim and Holt, 2013; Liu et al., 2014a, 2014b; Yi et al., 2010), where they appear to set the resting membrane potential.

Especially germane to this review are experiments by Yi et al. (2010) investigating the functional contribution of HCN channels to the SGN afferent dendrites in juvenile rats (7–14 days old). Through patch clamp recordings, they found that HCN channels set the resting membrane potential, decrease the decay time constant of the EPSP, and are positively regulated by intracellular cAMP. Immunofluorescence indicated that HCN1, 2, and 4 are the subunits expressed in the SGN afferent dendrites. Patch clamp recordings of the SGN afferent dendrites are consistent with patch clamp recordings of the SGN soma of wildtype and also adult HCN1 and HCN2 knockout mice (P40 or older; Kim and Holt, 2013) which also show that HCN channels (and especially HCN1) set the resting membrane potential and shorten rebound spike latency. Although HCN1 knockout mice show no differences in ABR thresholds or first peak amplitudes, they do show increased first peak latencies. Delayed latencies are consistent with a broadening of the EPSP due to loss of the HCN channels from the SGN afferent dendrites and/or somas. Identification of differences in subunit expression or abundance in specific subpopulations of afferent fibers would suggest an additional mechanism by which individual afferent fiber properties are determined.

4.4. Other voltage-gated ion channels and ion transporters

A plethora of voltage-gated calcium channels (VGCCs; reviewed generally in Simms and Zamponi, 2014) have also been identified in the SGNs and, in some cases, the SGN afferent dendrite specifically, using immunofluorescence, electrophysiology, and pharmacology (see Table 4). These include Ca_V1.2-3, and 2.1–3, and 3 (Lv et al., 2012, 2014), Ca_V1.2 and 2.1–2 (Roehm et al., 2008); Ca_V1.2-3, 2.1–3, 3.1 and 3.3 (Chen et al., 2011); Ca_V1.2-3 and 2.2–3 (Lopez et al., 2003). In principle, postsynaptic VGCCs would open in response to glutamate-mediated depolarization of the SGN afferent dendrites. Opening of VGCCs would contribute to depolarization of the SGN and increase the intracellular [Ca^{2+}]. Indeed, blockade of VGCCs in SGNs isolated from hearing mice show significant hyperpolarization of the resting membrane potential, suggesting that VGCCs are necessary for maintaining excitability (Lv et al., 2012). Consistent with this role, cochlear deletion of Ca_V1.2 (presumably from the SGNs) reduces ABR first peak amplitudes and also susceptibility to NIHL (Zuccotti et al., 2013). Relatedly, genetic deletion of CaV3.2 delays age-related loss of SGNs and cochlear function (Lei et al., 2011). Increases in intracellular [Ca^{2+}] through the opening of VGCCs could result in Ca^{2+} release from internal stores, modulation of other ion channels, induction of synaptic plasticity, and activation of transcription. Although not specifically investigated, work has suggested that VGCCs in SGNs may mediate such Ca^{2+}-dependent signaling pathways (Roehm et al., 2008).

Chloride channels (ClCs) are a superfamily of poorly understood ion channels that serve a diversity of roles in excitable (and non-excitable) cells (Stolting et al., 2014). The expression and function of ClCs in SGNs specifically has only recently been investigated. Inhibitors of ClCs hyperpolarize the resting membrane potential and reduce spontaneous AP firing in SGNs cultured from postnatal (1 or 2 days) and adult (1 or 2 months) mouse (Zhang et al., 2015). This work also specifically identified the TMEM16A (anoctamin-1 or ANO1), a Ca^{2+}-activated ClC, by immunofluorescence in SGNs cultured from mice (ages P1, P14, and P28) as mediating at least some of this Cl^- conductance. Importantly, SGNs cultured from TMEM16A knockout mice (aged less than 2 weeks) show reduced Ca^{2+}-activated Cl^- currents and altered AP firing. These findings suggest that spiking patterns in mature SGNs depend on the presence of specific ClCs.

Finally, the role of ion transporters and pumps in shaping membrane properties of the SGN afferent dendrite has been underinvestigated but likely depend on the Na^+,K^+-ATPase (NKA) α3 subunit (McLean et al., 2009). The NKA is an electrogenic ion pump that maintains the hyperpolarized membrane potential (Kaplan, 2002). Possible differences in distribution of the NKAα3 and/or its regulatory subunits among SGN afferent fiber types have not been specifically investigated but could confer differences in fiber responses.

5. Lateral efferent innervation of the type i spiral ganglion neurons

Postsynaptic excitability of the type I SGN afferent dendrites can also be shaped by synaptic input arising from efferent feedback originating in and around the (primarily ipsilateral) lateral superior

olive (Warr et al., 1997). Therefore, these lateral efferent terminals are an integrated component of the type I afferent signaling complex. Within the organ of Corti, the lateral efferent innervation of modiolar afferents is almost twice as large as that of pillar afferents (Liberman, 1980b; Liberman et al., 1990; Yin et al., 2014), suggesting that patterns of lateral efferent innervation might contribute to the heterogeneity of afferent fiber responses. Understanding the functional contributions of the lateral efferent system has been complicated by their neuroanatomy. First, due to their parallel anatomical course with the medial efferent system and lack of myelination, selectively lesioning or electrically stimulating the lateral efferent fibers is difficult (but see, Darrow et al., 2007; Le Prell et al., 2014; Liberman, 1990; Liberman et al., 2014; Yin et al., 2014; Zheng et al., 1999). Second, the neurons of the lateral efferent system differ in their sites of central origination and degree of arborization in the periphery (Brown, 1987; Warr et al., 1997). Third, the lateral efferent system utilizes a variety of neurotransmitters (reviewed in Eybalin, 1993).

Given their neuroanatomy, it is perhaps not surprisingthat stimulation of LOC efferents via the superior colliculus can produce either long lasting enhancement or suppression of auditory nerve activity (Groff and Liberman, 2003). Importantly, this and much other work examining the effects of the lateral efferent system on afferent output investigates changes at the level of the central afferent process. Presumably the lateral efferent system exerts changes in afferent excitability at sites of synaptic contact on the peripheral SGN afferent dendrite and may vary considerably based on efferent terminal morphology and cytochemistry. This section reviews literature on the three main neurotransmitters of the lateral efferent system, dopamine (DA), acetylcholine (ACh), and GABA, focusing on molecular effects that directly regulate SGN afferent dendrite excitability (see Table 5). Of course, given the diversity of neurotransmitter receptors, these neurotransmitters could also exert indirect effects by acting on autoreceptors on the efferent terminals or receptors present on the IHC. More extensive reviews of the cochlear efferent system are provided elsewhere (Nouvian et al., 2015; Ruel et al., 2007).

5.1. Acetylcholine

Acetylcholine is a major neurotransmitter of the lateral efferent system (Eybalin, 1993). Functionally, ACh application increases afferent spiking recorded from just below the IHCs of the intact guinea pig cochlea (Arnold et al., 1998; Felix and Ehrenberger, 1992). Moreover, ACh application enhances glutamate-induced afferent spiking (Felix and Ehrenberger, 1992), suggesting ACh exerts its effect on the postsynaptic responsiveness of the SGN afferent dendrites. ACh released by efferent terminals would most directly regulate excitability by activating ACh receptors (AChRs) present on the SGN afferent dendrites. Like many other ligand-activated neurotransmitter receptors, AChRs can be either ionotropic (nicotinic receptors, nAChRs) or metabotropic (muscarinic receptors, mAChRs), and both nAChRs and mAChRs have been identified in SGNs (summarized below and see Table 5).

The neuronal nAChRs comprise eight α-like subunits, α2-7 and 9–10, and three β subunits, β2-4 (Albuquerque et al., 2009). The diversity of subunit types and assembly into homo- or heteropentamers tailors function of nAChRs in the cells that express them. mRNA expression of the α5-7, and β2-3 nAChR subunits were identified in micro-dissected SGNs from the rat cochlea (Morley et al., 1998). Immunoreactivity for α and β nAChR subunits was also found in human adult SGN somas (Popa et al., 2000). Subsequent immunocytochemistry and RT-PCR revealed reduced nAChR β2 subunit protein and transcript expression in SGNs from old (24–32 months) compared to young (2–3 months) mice (Tang et al., 2014). Mice lacking the nAChR β2 subunit show a significant reduction in the number of SGNs compared to wildtype mice at 8 months of age (Bao et al., 2005), suggesting that this subunit is somehow neuroprotective. However, validation of this phenotype is complicated by possible additional alterations in glucocorticoid signaling (Shen et al., 2011).

The mAChRs comprise a family of five related G protein-coupled receptors (GPCRs): three of these receptor subtypes (M_1, M_3 and M_5) couple to G proteins of the $G_{\alpha q/11}$ family of (stimulatory) G proteins whereas the other two (M_2 and M_4) couple to $G_{\alpha i/o}$ family of (inhibitory) G proteins (Kruse et al., 2014; Wess, 1996). SGNs isolated from rat (aged P1–P7) show that ACh application induces a mAChR-dependent inward current and an increase in intracellular [Ca^{2+}] (Ito and Dulon, 2002; Rome et al., 1999). By far the most extensive investigation of mAChR localization and function in the cochlea was carried out by Maison et al. (2010). Although M_3 transcript (Safieddine et al., 1996) and M_3 and M_5 protein (Khan et al., 2002) were previously identified in SGNs, Maison and colleagues found no auditory deficits in M_3 and M_5 knockout mice (2010). M_2 and M_4 transcripts were identified in micro-dissected SGNs from mice and M_2 was immunofluorescently localized to olivocochlear fibers beneath the IHCs (Maison et al., 2010). Loss of either M_2 or M_4 or both M_2 and M_4 elevated ABR thresholds (at frequencies between 22 and 45 kHz) and reduced suprathreshold neural responses (at frequencies $\geq$ 16 kHz). M_2/M_4 double knockouts showed greater resistance to noise-induced temporary and permanent threshold shifts. These results suggest that muscarinic signaling via inhibitory signaling pathways serves to increase SGN excitability. Further work needs to be done to understand how this signaling might homeostatically contribute to the heterogeneity of afferent fiber types.

5.2. Dopamine

Dopamine is another neurotransmitter of the lateral efferent system (Eybalin, 1993; Gil-Loyzaga, 1995). Immunocytochemistry suggests that the cholinergic and dopaminergic efferent fibers are separate groups and that cholinergic fibers outnumber dopaminergic fibers (Darrow et al., 2006b; Niu et al., 2004). Nevertheless, delineating the specific effects of ACh and DA as neurotransmitters of the lateral efferent system has proven difficult, and the effects of DA have proven particularly intractable (summarized in Maison et al., 2012).

Some experiments suggest that DA reduces afferent activity. DA perfusion into the cochlea causes a reduction in evoked afferent fiber firing rate recorded at the base of the IHCs in the adult guinea pig (Oestreicher et al., 1997). Consistent with these findings, DA perfusion into the adult guinea pig cochlea causes an increase in the CAP threshold and decrease in the CAP amplitude (Ruel et al., 2001). Finally, blockade of DA transporters increases cochlear concentrations of DA and decreases the CAP amplitude (Ruel et al., 2006). This inhibition of activity may arise from inhibition of voltage-gated sodium currents present on the SGNs. Specifically, patch clamp recordings from SGNs isolated from neonatal mice (P0-5) and rats (P8-9) show that voltage-gated sodium currents are inhibited by either DA application or activation of dopamine receptors (Sun and Salvi, 2001; Valdes-Baizabal et al., 2015). On the other hand, the effects of DA are likely not so straightforward. Ablation of the dopaminergic lateral efferent system by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) administration, a neurotoxin specific for dopaminergic neurons, caused a decrease in the CAP amplitude, suggesting that DA normally acts to stimulate afferent activity (Le Prell et al., 2005; Le Prell et al., 2014).

Differences in DA receptor expression among subpopulations of afferent fibers may explain the controversial effects of DA. There are

5 known DA receptors (D1-5). Canonically, the D1-like DA receptors (D1 and D5) are postsynaptic and activate the stimulatory family of G proteins to increase cAMP production by adenylyl cyclase. The D2-like DA receptors (D2, D3, and D4) are expressed pre- and postsynapticaly and activate the inhibitory family of G proteins to inhibit adenylyl cyclase (Beaulieu and Gainetdinov, 2011). Although an initial study identified all 5 DA receptors in the SGN soma of adult rat (Inoue et al., 2006), more recent work suggests the presence of D1 (Maison et al., 2012; Niu and Canlon, 2006) and D2 (Maison et al., 2012) specifically on the SGN afferent dendrites contacting the IHCs.

To investigate receptor specific effects of DA, Garrett and colleagues examined the effects of D1/5, D2, and D3 receptor agonists and antagonists on CAP amplitudes (2011). In this study, D1/5 agonists decreased CAP amplitude while antagonists had no effect; D2 agonists had little effect whereas D2 antagonists decreased CAP amplitude; and D3 agonists and antagonists had no effect. Consistent with these findings, D1 knockout mice show reduced ABR thresholds and increased suprathreshold ABR amplitudes (Maison et al., 2012). D2 knockout mice show increased ABR thresholds and decreased suprathreshold ABR amplitudes (Maison et al., 2012). In contrast to the findings of Garrett and colleagues, Niu and Canlon observed a decrease in CAP amplitude and increase in the CAP threshold in response to D1/5 receptor antagonists (2006), d'Aldin and colleagues found an increase in CAP amplitude after D2/3 agonist perfusion (1995), and Ruel and colleagues showed that D1 and D2 antagonists (as well as DA) decreased CAP amplitudes (2001).

Interpreting the role of DA receptors is further complicated by the possible expression of DA receptors on the OHCs (Garrett et al., 2011; Maison et al., 2012; Wang et al., 2014a) as well as the lateral efferent presynaptic terminals (Gaborjan et al., 1999; Halmos et al., 2005). Additionally, DA receptor antagonism may abolish neuroprotective effects of DA and complicate interpretation of afferent fiber activity (Ruel et al., 2001). Finally, recent work documenting the DA-mediated inhibition of Na^+ currents in cultured SGNs, used pharmacology to provide evidence that inhibition resulted from D2-mediated activation of $G_{\alpha q}$, which activates phospholipase C and ultimately leads to sodium channel phosphorylation (Valdes-Baizabal et al., 2015). Activation of $G_{\alpha q}$ normally occurs via D1 receptors but may also result from D1:D2 heterodimers (Beaulieu and Gainetdinov, 2011). Thus, DA receptor signaling in the cochlea may be additionally complicated by unconventional G protein coupling and/or dopamine receptor heterodimers that alter pharmacology and intracellular signaling pathways.

5.3. GABA

GABA, the major inhibitory neurotransmitter of the CNS, is another neurotransmitter of the lateral efferent system (Eybalin, 1993; Gil-Loyzaga, 1995). GABA immunoreactivity in lateral efferent terminals is extensively colocalized with ACh (Maison et al., 2003) and appears to modulate afferent excitability. GABA can exert effects on two classes of GABA receptors (GABARs). The $GABA_A$ receptors are ionotropic receptors consisting of pentamers of 19 possible subunits that form a ligand-gated ion channel (Barnard et al., 1998; Sigel and Steinmann, 2012). In addition to activation of $GABA_A$ receptors, GABA can also activate $GABA_B$ receptors. $GABA_B$ receptors are metabotropic receptors consisting of B1 and B2 subunits linked to inhibitory family of G proteins. In the CNS, activation of $GABA_B$ receptors tends to inhibit presynaptic calcium channels, activate postsynaptic potassium channels, and inhibit adenylyl cyclase (Benarroch, 2012; Bettler et al., 1998).

Evidence implicates the $GABA_A$ receptors in mediating the inhibitory effect of GABA in the SGNs specifically and the cochlea more generally. First, $GABA_A$ receptor immunoreactivity was detected in the SGN somas in the adult rat (Yamamoto et al., 2002; Yang et al., 2008) and mouse (Maison et al., 2006; Tang et al., 2014) and putative SGN afferent dendrites (Yamamoto et al., 2002) in the adult rat cochlea. GABA-mediated (Cl^-) currents have been recorded from SGNs isolated from neonatal (E14-P5) mice (Lin et al., 2000), neonatal (P3) rat (Malgrange et al., 1997), and adult guinea pig (Nakagawa et al., 2005). Based on pharmacology (Lin et al., 2000; Malgrange et al., 1997; Nakagawa et al., 2005), these currents are likely mediated by $GABA_A$ receptors. Second, recordings of afferent activity just below the IHCs from high frequency regions of the intact guinea pig cochlea, show that GABA application decreases Glu- and ACh-induced increases in afferent spiking specifically through activation of $GABA_A$ but not $GABA_B$ (Arnold et al., 1998; Felix and Ehrenberger, 1992). Administration of a $GABA_A$ agonist protected adult mice from noise-induced ABR threshold shifts (Murashita et al., 2007) and guinea pigs from kainite-induced CAP threshold shifts (Sakai et al., 2008). These neuroprotective effects were attributed to $GABA_A$ but not $GABA_B$ (Sakai et al., 2008). Finally, reduced expression of $GABA_A$ has been associated with age-related hearing loss (Tang et al., 2014).

The inhibitory effects of $GABA_A$ activation are consistent with recent work showing that, at least in cultured SGNs, the intracellular [Cl^-] is dramatically reduced with maturation such that the Cl^--permeable channels allow the hyperpolarizing influx of Cl^- (Zhang et al., 2015). If a similar electrochemical gradient is present in the mature SGN afferent dendrites, then activation of $GABA_A$ receptors is likely inhibitory. Activation of inhibitory $GABA_A$-mediated currents would be consistent with GABA-mediated decreases in Glu- and ACh-induced afferent spiking frequency and also protection from NIHL. Left to be resolved, however, is the curious finding that GABA application has no effect on spontaneous afferent activity (Arnold et al., 1998; Felix and Ehrenberger, 1992).

Together these data suggest that GABA receptors, especially $GABA_A$, are positioned to inhibit afferent activity and provide neuroprotection in cases of overstimulation. $GABA_A$ knockout mice would, therefore, be expected to show reduced ABR thresholds and increased susceptibility to NIHL. Investigation of $GABA_A$ receptor knockout mice does not cleanly support this prediction, and, in fact, $GABA_A$-mediated signaling appears to be involved in the maintenance of afferent innervation rather than modulation of afferent excitability specifically (Maison et al., 2006).

Although less investigated, $GABA_B$ receptors have also been identified in SGNs isolated from neonatal mice (P0–P5) and $GABA_B$ agonists appear to alter intracellular [Ca^{2+}] (Lin et al., 2000). GFP-tagged $GABA_{B1}$ localizes to the SGNs and likely their afferent terminals (Maison et al., 2009). As in $GABA_A$ receptor knockout mice, no clear phenotype could be specifically attributed to the type I afferent SGNs in $GABA_{B1}$ knockout mice (Maison et al., 2009). Of course, in both cases, it may be that the assays employed did not activate GABAergic transmission and, therefore, missed a phenotype.

6. The afferent signaling complex

Extensive work examining glutamatergic signaling, voltage-gated ion channels and lateral efferent innervation of the SGNs and their peripheral processes is elucidating the molecular architecture of the SGN afferent dendrite and neighboring structures (see Table 6). The cellular and molecular organization of these structures is shown in Fig. 1. Immunofluorescent images show the sensory IHCs (green) contacted by the type I afferent dendrites (red, Fig. 1A). In turn, these afferent dendrites (red) are contacted by lateral efferent terminals (green, Fig. 1B). The molecular architecture of these and neighboring structures is schematized in Fig. 1C

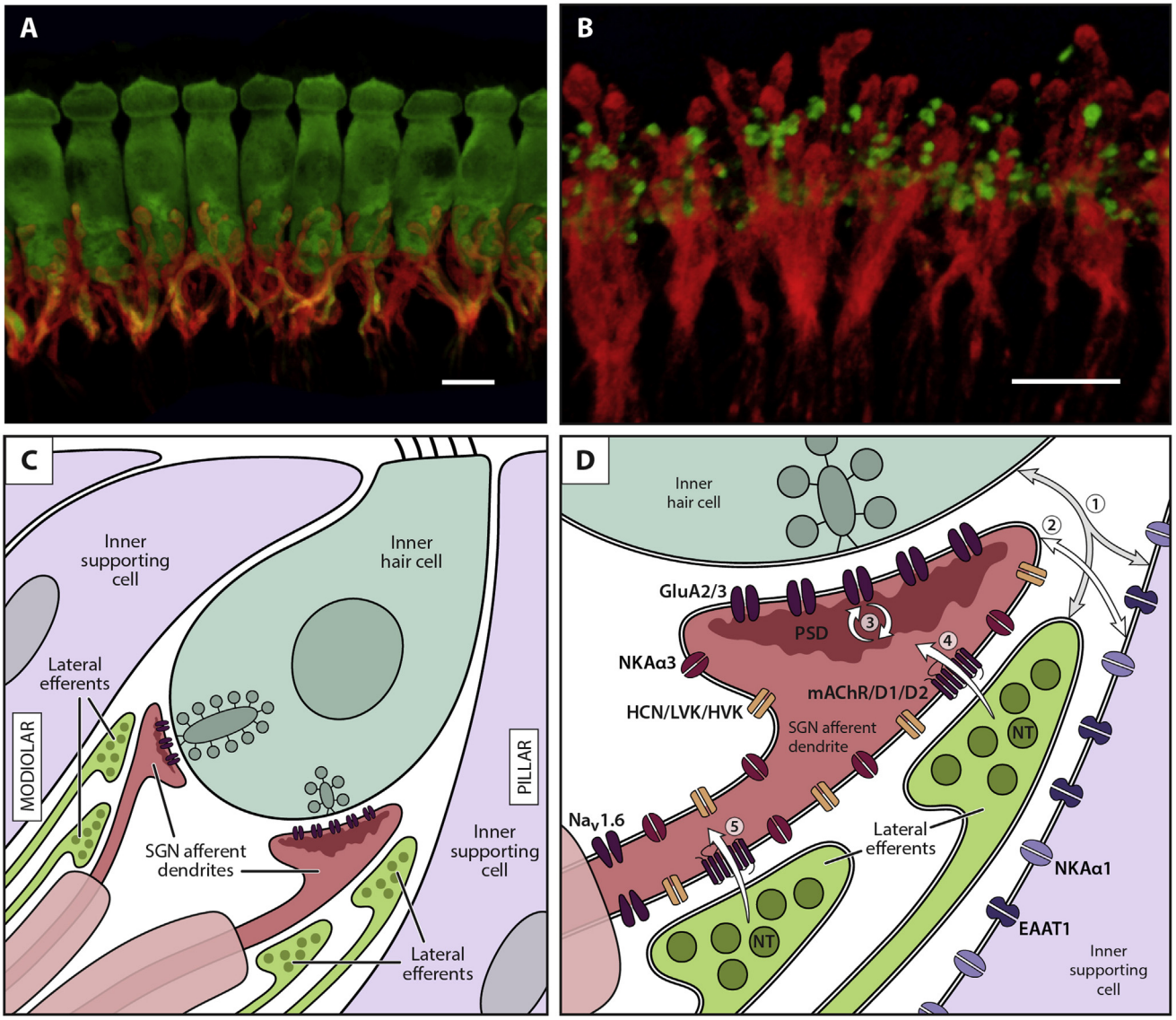

Fig. 1. The type I afferent signaling complex. A. 3D reconstruction of a z-stack of confocal micrographs showing the inner hair cells (green, calretinin) and peripheral dendrites of the spiral ganglion neurons (red, Na^+,K^+-ATPase α3). B. 3D reconstruction of a stack of confocal micrographs showing the peripheral dendrites of the spiral ganglion neurons (red, Na^+,K^+-ATPase α3) contacted by terminals of the lateral olivocochlear efferents (green, synapsin). Scale bars equal 10 μm (and, therefore, panel B is at a higher magnification than panel A). Organs of Corti were isolated from C57BL/6 mice aged postnatal day 20 and prepared for immunostaining as described previously (McLean et al., 2009) C. Schematic of the type I afferent signaling complex showing an inner hair cell, the peripheral terminals of the spiral ganglion neuron afferent dendrites, the terminals of the lateral efferents, and the inner supporting cells. D. Schematic diagram of the auditory signaling complex with identified molecules labeled. Possible interactions as part of the afferent signaling complex are numbered and include 1) reciprocal regulation between the inner hair cells and the inner supporting cells and also lateral efferent terminals; 2) reciprocal regulation of the lateral efferent terminals and inner supporting cells; 3) regulation of GluA2/3 trafficking and structure of the postsynaptic density (PSD); and 4 and 5) metabotropic lateral efferent regulation of excitatory postsynaptic potential (4) and action potential (5) generation. Evidence of these interactions and areas of future research are described in more detail in Section 6. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and D. Observations of pre- and postsynaptic differences in the molecular structure of the IHC-SGN afferent synapses provide evidence that differences in afferent fiber responses originate peripherally (highlighted in Section 1). While some of these functional differences are conferred by differences structure and in molecular composition, others likely emerge less conspicuously from interactions of the inner hair cells, the SGN afferent dendrites, the terminals of the lateral efferents, and the neighboring inner supporting cells. These structures collectively comprise the afferent signaling complex (depicted in Fig. 1). The functional interaction of components of this complex together determine afferent dendrite excitability and, in turn, afferent fiber responses. With these functional interactions in mind, areas of future research investigating the afferent signaling complex are indicated in this Section.

6.1. Glutamatergic signaling

Extensive evidence (reviewed in Section 2.1 and see Table 1) indicates that GluAs, and especially GluA2 (and perhaps also GluA3), mediate the EPSP at the SGN afferent dendrite. The correlation between pillar-modiolar gradients in GluA2 distribution with pillar-modiolar gradients in fiber properties, suggest that regulated GluA2 expression (together with presynaptic mechanisms) contributes to the heterogeneity of fiber types (Liberman et al., 2011). Establishing, maintaining, and modifying GluA2 expression within a single SGN afferent dendrite or as gradients across SGN afferent

dendrites is no doubt coordinated by components of the SGN PSD. Many of these components have yet to be identified or investigated. Given the abundance of GluA2 in the SGN postsynapse, first candidates for future investigation include proteins like GRIP (glutamate receptor interacting protein), PICK (protein interacting with C-kinase), and NSF (N-ethylmaleimide-sensitive factor) that directly interact with GluA2 to regulate receptor trafficking (Anggono and Huganir, 2012; Huganir and Nicoll, 2013).

The molecular organization of the SGN PSD is no doubt also regulated by integrated properties of the afferent signaling complex. Given that Ca^{2+} is a critical regulator of the PSD in the CNS, Ca^{2+}-permeable channels of the SGN afferent dendrite may exert organizational effects on the SGN PSD that have yet been uninvestigated. These Ca^{2+}-permeable channels include certain glutamate receptors (GluA2 or NMDA, reviewed in Section 2.1 and 2.3), VGCCs (reviewed in Section 4.4), and also receptors of lateral efferent neurotransmitters (like nAChRs, reviewed in Section 5.1). Identification of gradients in the molecular identities and biophysical properties of glutamate receptors in the SGN PSD would provide mechanistic insight into the regulation of GluA2 gradients that correlate with fiber properties (Liberman et al., 2011). Additionally, the functional contribution and subcellular localization of VGCCs in the SGN afferent dendrites requires further examination. Interestingly, while IHCs rely largely on one class of VGCCs, $Ca_V1.3$, SGNs express multiple Ca_Vs, which together may mediate a variety of Ca^{2+}-dependent functions (Lv et al., 2014), including organization of the SGN PSD. In addition to or perhaps as part of Ca^{2+}-dependent regulation of the SGN PSD, metabotropic cascades initiated by the lateral efferent neurotransmitters may also serve to organize and/or maintain SGN PSDs and need to be investigated further. This role is supported by the observation that GluA2 gradients collapse following ablation of lateral efferent innervation (Yin et al., 2014).

The time course of glutamate removal from the synaptic cleft between the SGN and IHC will also shape glutamatergic signaling. A variety of evidence indicates that glutamate transporters expressed in the inner supporting cells surrounding the IHC-SGN synapses may not play a critical role in auditory function under conditions of quiet or moderate noise levels (reviewed in Section 3). Elegant work in the bullfrog papilla showed that enlarged extracellular spaces contributes more to glutamatergic signaling than active transport (Graydon et al., 2014). In mammals, it may also be that the spacing surrounding the IHC-SGN synapse allows sufficiently rapid diffusion of glutamate. This conclusion is indirectly supported by findings from type I vestibular hair cells. In these synapses, diffusion of glutamate from the synaptic cleft is enormously hindered by the afferent calyx ending that encapsulates the hair cell and glutamate spillover indeed influences synaptic transmission (Sadeghi et al., 2014).

Nonetheless, a variety of findings indicate that the inner supporting cells are not passive components of the afferent signaling complex. First, recent work indicates that inner supporting cells in the developing cochlea release adenosine 5′-triphosphate (ATP), which initiates Ca^{2+} spikes in IHCs and triggers bursts of APs in SGNs (Tritsch and Bergles, 2010; Tritsch et al., 2007). Second, inner supporting cells are required for trophic survival of the SGNs and their afferent dendrites, even after loss of the IHCs (Zilberstein et al., 2012). Moreover, metabolism of the inner supporting cells (ISCs) may be reciprocally modulated by other components of the afferent signaling complex. For example, the inner supporting cells rely on EAAT1 (Glowatzki et al., 2006) and likely NKAα1 (McLean et al., 2009) for efficient clearance of glutamate and also extracellular K^+. Elsewhere in the body the activity of both of these molecules is modified by molecular cascades that may also occur in the afferent signaling complex. For example, glutamate increases EAAT1 transport activity and protein kinase C (PKC) activation decreases EAAT1 transport activity (Sattler and Rothstein, 2006). NKAαs are inhibited by dopamine receptor signaling (Reinhard et al., 2013). Thus, both afferent and efferent neurotransmitters could influence EAAT1-and NKAα1-dependent transport activity of the inner supporting cells. Regulation of transport efficiency might be especially important during acoustic overexposure, when glutamate clearance is likely insufficient and leads to excitotoxic loss of afferent synapses (Pujol and Puel, 1999) and/or as part of age-related hearing loss. Ultimately, various roles essential to afferent synapse development and function can be ascribed to the inner supporting cells as part of the afferent signal complex and warrant further investigation.

6.2. Voltage-gated ion channels

The basic properties and heterogeneity of afferent fiber types will also be conferred by the complement and distribution of voltage-gated ion channels within and among the SGN afferent dendrites (see Tables 2–4). In general, voltage-gated ion channels that minimize Na^+ channel inactivation and increase membrane repolarization enable fast and reliable spiking and are likely in place in all SGNs as well as their afferent dendrites. These channels minimally include $Na_V1.6$ and likely K_V3 members based on their expression in the SGNs (reviewed in Sections 4.1 and 4.2) and insights from neurons of the auditory brainstem (reviewed recently in Golding and Oertel, 2012; Johnston et al., 2010; Kaczmarek et al., 2005; Oak and Yi, 2014). Following AP initiation, membrane repolarization in the SGN afferent dendrite will be the responsibility of high voltage-activated K_V channels. K_V3 channels are especially prominent in neurons able to fire sustained rates at high frequencies because they enable fast repolarization. K_V3 channels are expressed throughout the auditory pathway including SGNs (reviewed in Section 4.2). Finally, variations in auditory fiber threshold sensitivities and firing rates are conferred by voltage-gated ion channels that set the resting membrane potential and regulate membrane repolarization between APs. The distributions and subunit configurations of these channels may, therefore, be more heterogeneous within the SGNs and their afferent dendrites. Again, based on their expression in the SGNs and insights from neurons of the auditory brainstem, low voltage-activated potassium channels, especially K_V1, and HCN channels, likely serve to set the resting membrane potential and influence threshold sensitivities. Both of these channels have been identified throughout the auditory pathway and in isolated SGNs (reviewed in Section 4.2). HCN channels have been particularly characterized using patch clamp recordings of the SGN afferent dendrite (Yi et al., 2010). Finally K_V2 has been shown to influence firing frequency in neurons of the auditory brainstem (Johnston et al., 2008) and is expressed in the SGNs (reviewed in Section 4.2).

Because voltage-gated ion channels contribute to the intrinsic properties that regulate SGN afferent dendrite excitability, concerted effort should be placed on identifying and localizing their distribution within and among the SGN afferent dendrites. Moreover, it is becoming increasingly appreciated that intracellular modification of ion channels, especially phosphorylation, alters their biophysical properties, distribution, and membrane trafficking in cell-specific and even compartmentally-specific ways (Cerda and Trimmer, 2010). Thus, functional properties of a similar repertoire of ion channels may be post-translationally modified to give rise to the observed heterogeneity in afferent fiber thresholds and spontaneous firing rates. Lateral efferent innervation could exert such metabotropic modulation of SGN afferent dendrite ion channels. Such influence is perhaps indicated by previous work showing that lateral efferent innervation balances bilateral afferent

excitability (Darrow et al., 2006a). Additional modification of ion channel function may also result from hetero-multimerization, which has been postulated to occur in SGNs (Wang et al., 2013). Relatedly, the NKAα3, which is abundantly expressed in the SGN afferent terminals (McLean et al., 2009), is subject to metabotropic modification that can influence the resting membrane potential and regulate membrane repolarization (Reinhard et al., 2013). Ultimately, careful dissection of voltage-gated ion channel and ion transporter distribution, function, and intracellular modification in the SGN afferent dendrites is necessary and should be facilitated by the plethora of ion channel gene knockout and knock in models that exist (Meredith, 2015).

6.3. Lateral efferent innervation

The neurotransmitters of the lateral efferent system include ACh, DA, and GABA among others. Via ionotropic and metabotropic receptors these neurotransmitters exert excitatory and inhibitory regulation of SGN afferent dendrite excitability. The receptors of particular functional interest appear to be the mAChRs M_2 and M_4, the DA receptors D1 and D2, and $GABA_A$ (reviewed in Section 4 and see Table 5). Differing sites of efferent terminal contact may indicate that some lateral efferents, those contacting the SGN afferent bouton, may serve to modulate EPSP generation, whereas other terminals, those contacting the heminode of the SGN afferent dendrite, may serve to modulate action potential generation (Fig. 1D). More generally, lateral efferents appear to provide trophic support of the SGN afferent dendrites (Zilberstein et al., 2012) and organize GluA receptors in the SGN afferent dendrites (Yin et al., 2014). In turn, lateral efferent activity is likely also regulated locally as part of the afferent signaling complex. For example, mGluR-mediated modulation of lateral efferent activity in the cochlea has been postulated (Doleviczenyi et al., 2005). Unfortunately, the molecular mechanisms that functionally couple the lateral efferent terminals to other components of the afferent signaling complex are still mostly unknown and may be additionally difficult to resolve pharmacologically because of the possible expression of receptor heteromers (see Section 4.2). Ultimately, examining the function of lateral efferents as part of the afferent signaling complex has been enormously hindered by the inability to probe the lateral efferents at their sites of synaptic contact with the SGN afferent dendrites. Considerable effort should be placed on the development of new tools, such as optogenetic methods to stimulate and inhibit specific neurotransmitter pathways, to examine the lateral efferent synapses within the afferent signaling complex.

7. Conclusion

Function of the type I SGN afferent synapses, excitability of the SGN afferent dendrites, and ultimately the heterogeneity of the auditory afferent fiber responses will be conferred by closely associated peripheral structures that together comprise the type I afferent signaling complex. In the cochlea, these structures include the presynaptic specializations of the inner hair cells, the SGN afferent dendrites, the terminals of the lateral efferents, and the neighboring inner supporting cells. Existing research indicates that this complex regulates maturation, modulation, and trophic support of the auditory afferent synapses and their dendrites.

Much exciting work is yet ahead to discover the molecular machinery that underlies the functional interactions of this afferent signaling complex. Identifying these interactions will provide essential new insights into the molecular sources of afferent fiber heterogeneity that are necessary for normal hearing. Furthermore, a growing body of research has focused attention on the particular vulnerability of the afferent synapses between the IHCs and SGNs as part of hearing loss. In auditory synaptopathies (Moser et al., 2013), malfunctioning inner hair cell ribbon synapses cause a variety of both genetic and acquired hearing disorders. In hidden hearing loss (Kujawa and Liberman, 2015), noise-induced and age-related excitotoxic loss of the SGN afferent dendrites and synapses contributes to hearing difficulties that can go undiagnosed by traditional audiometry. In both cases, pathophysiology of the afferent synapses occurs within a larger cellular and molecular framework that collectively determines excitability of the afferent fibers and provides extracellular support of the afferent synapses. Better understanding of the integrated processes of this afferent signaling complex will lead to better diagnosis and treatment of these various hearing disorders.

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